REMARKS

Claims 1-9 are pending. Claims 1-8 have been withdrawn from further consideration as being drawn to non-elected inventions. Claim 9 has been amended to address examiner's objections to the recitation of "or a specific binding partner" as reading on a non-elected invention, as well as to obviate the rejections under 35 U.S.C. 112 for being indefinite. Support for the amendment to claim 9 can be found on page 2, lines 31-34, page 3, lines 1-2, page 10, lines 23-31 and page 11, line 1. Thus, amended claim 9 remains under consideration.

The amendments proposed herein are clearly indicated in the attachment entitled "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

No new matter has been added by way of this amendment. Reconsideration of this application is respectfully requested.

Claim Objections

Examiner has objected to claim 9, in part, for reciting "or a specific binding partner", which examiner alleges reads on a non-elected invention as per the restriction requirement. Applicants have amended claim 9 to delete the phrase "or a specific binding partner", thus obviating examiner's objection.

Claim Rejections under 35 USC §112

Examiner has rejected claim 9 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Applicants respectfully traverse examiner's rejections. Claim 9 has been amended to more distinctly claim and particularly point out that which Applicants regard as their invention, thus obviating the examiner's rejections.

Claim 9 has been rejected under 35 U.S.C 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly

connected, to use the invention as claimed.

Applicants respectfully traverse Examiner's rejection and herein provide a declaration under 37 CFR 1.132 which attests to protocols and compilation of data obtained from a series of experiments performed in the laboratory of the inventor. These experiments provide confirmatory evidence that small molecule inhibitors of Gli1, in particular, small interfering RNAs, inhibit proliferation of tumor cells. These data support the earlier studies provided in the instant application, whereby the inventor has provided evidence that Gli1 acts as a target and mediator of Shh signaling, and that ectopic expression of Gli1 in the epidermal ectoderm of frog embryos results in tumor formation. More specifically, activation of Shh signaling leads to Gli1 expression in the epidermis and results in basal cell carcinoma. Taking his studies one step further, the inventor also addressed the possibility that Gli1 activation and ectopic expression of Gli1 could play a role in the development of adult sporadic BCC, and assayed spontaneously occurring human BCC's for Gli1 expression. In situ hybridization studies showed that elevated levels of Gli1 expression were observed in all but one sample tested, thus strengthening his position as to a relationship between Gli1 expression and its role in tumorigenesis.

Examiner alleges that the specification does not provide guidance and evidence that compositions comprising inhibitors of the expression and activity of Gli1 in the instant application would invoke a therapeutic response. Applicant respectfully requests entry of the data provided in the declaration under 37 CFR 1.132 into the instant application as supportive evidence herewith. Also provided herein as Exhibit B are references that pertain to the use of small interfering RNA molecules for therapeutic intervention. Such references clearly demonstrate the use of these molecules for various disorders. A skilled artisan would be cognizant of such references and as such would be fully able to practice the methods of the present invention.

Moreover, as to Examiner's comments that the specification provides no guidance as to any clinically significant chang in S phase activity of a target cell mass, Applicant wishes to direct the Examiner's attention once again to the experimental

data provided in the declaration signed by the inventor. The studies performed in Applicant's own laboratory with the small RNA molecules that inhibit Gli1 expression and activity (siRNA) demonstrated that tumor cell proliferation was inhibited when cells were transfected with these small interfering RNA molecules specific for Gli1. Furthermore, the experiments were done using BrdU incorporation as a measure of tumor cell proliferation, or the inhibition thereof. The nature of these studies calls for incorporation of BrdU into cells during the S phase of the cell cycle. Thus, cells that are actively proliferating would show significant BrdU incorporation, whereas cells that were not actively proliferating would demonstrate diminished proliferation as shown by a decrease in BrdU incorporation. The results of these studies demonstrated that the cells transfected with the small interfering RNA molecules specific for Gli1 were significantly inhibited in terms of cellular proliferation as compared to cells transfected with small RNA molecules not specific for Gli1 (control).

With respect to Examiner's comments regarding other clinically relevant features of pathology, and the fact that drug discovery in the area of cancer research is not predictive, Applicant respectfully notes Examiner's concerns, but also wishes to draw the Examiner's attention to the fact that as noted in section 2107.03 (I) of the MPEP:

> " The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use. *Nelson v. Bowler*, 626 F.2d 853, 857, 206 USPQ 881, 884 (CCPA 1980)."

Furthermore, the Examiner points to the fact that model systems are not always predictive of the potential outcome in humans, as evidenced by the low number of drugs approved by the FDA. Though Applicants agree in part with this statement made by Examiner, Applicant respectfully would also like to point out that the issues of safety and tolerance of drugs under development for cancer therapy, as

noted in the office action, are relevant features related to the drug development process and the FDA, and not to the immediate issues related to patentabilty of the present invention.

Furthermore, Applicant directs the Examiner's attention to the fact that as noted in the specification on page 3, lines 2-5 it is envisioned that "....suitable pharmaceutical compositions could be administered by a variety of routes, including topical, oral, parenteral, intrathecal, intranasal and the like, at a dosage level and schedule that may be determined by the clinician in accordance with the particular condition of the patient."

Moreover, on page 10, lines 27-31 through page 11, lines 1-5, "...Gli1 or its binding partners or other ligands or agents exhibiting either mimicry or antagonism to it or control over its production, may be prepared in pharmaceutical compositions, with a suitable carrier and at a strength effective for administration by various means to a patient experiencing an adverse medical condition associated with Gli1 activity or expression..."

Applicant draws the Examiner's attention to the fact that given the level of knowledge in the area of pharmaceutical drug development, and with particular reference to pharmaceutical compositions and formulations in general use, one of skill in the art could effectively combine the Gli1 inhibitors claimed in the present invention with suitable carriers to achieve the desired result. Applicant notes that such a process would not pose an undue burden to a skilled artisan. Furthermore, Applicant has also provided evidence as Exhibit B in the declaration under CFR 1.132 that, as related to the particular small molecule antagonists described in the data submitted, a skilled artisan would be able to practice the invention given the level of knowledge in the art at the time the invention was made.

Applicant respectfully requests withdrawal of this rejection for the above reasons.

Claim Rejections under 35 USC §102

The Examiner has rejected claim 9 under 35 U.S.C. 102(b) as being anticipated by Yamada et al (US patent No. 5,247,070, 1993).

Applicant respectfully traverses this rejection for the following reasons. Applicant has amended claim 9 to clarify the pharmaceutical compositions envisioned by the present invention. Applicant has removed the terms "complements or fragments thereof, mixtures thereof" in order to overcome the rejection as previously noted under U.S.C. 112 and to more clearly define what Applicant considers to be the invention.

Furthermore, Applicant claims pharmaceutical compositions comprising pharmaceutically acceptable carriers and antagonists of Gli1 expression/function for the treatment of cellular debilitations caused by the presence of sporadic basal cell carcinoma.

At best, the Examiner's interpretation of Yamada et al., in US Patent No. 5,247,070, appears to be that the patent provides a teaching of a group of polypeptides which comprehend the compositions of the present invention. In fact, the Yamada et al. disclosure profoundly lacks any teaching of an association of the patentees' polypeptides with the active agents of the present invention ie. an effect on expression of Gli1 and a corresponding effect on cellular debilitations caused by sporadic basal cell carcinoma. More particularly, the Yamada et al. polypeptides are even further limited to tumor necrosis polypeptides, having specific amino acid sequences represented by specific sequence identifiers and teach away from the materials and agents of the present invention.

Yamada et al. neither teach nor suggest compositions comprising Gli1 antagonists, nor do they teach such compositions for the treatment of cellular debilitations caused by the presence of sporadic basal cell carcinoma.

The important aspects of Applicant's invention ar lacking from Yamada t al. and

can only be supplemented, if at all, by resorting to Applicant's own disclosure, which it is submitted, is impermissible hindsight reconstruction.

Therefore, the polypeptides of the compositions claimed by Yamada et al. do not have any relationship to the composition of the present invention.

For these reasons, the rejection of claim 9 under 35 U.S.C. 102(b) is improperly based. Applicant respectfully requests withdrawal of the rejection.

Fees

No fees are believed to be necessitated by this response. However, should this be in error, authorization is hereby given to charge Deposit Account no. 11-1153 for any underpayment, or to credit any overpayments.

Conclusion

Applicants believe that the outstanding rejections based on 35 U.S.C. §112 and 35 U.S.C. § 102(b) have been overcome by the amendments and arguments presented above. Thus, reconsideration and withdrawal of the outstanding grounds of rejection, and early allowance of the claims as amended is believed to be in order and is courteously solicited.

In the event that there are any questions concerning this amendment, or the application in general, the Examiner is respectfully urged to telephone the undersigned at the number listed below, so that prosecution of the application may be expedited.

Respectfully submitted,

Veronica Mallon

Veronica Mallon, Ph.D.
Agent for Applicant(s)
Registration No. 52,491

KLAUBER & JACKSON
411 Hack nsack Avenue
Hackensack, NJ 07601
(201) 487-5800

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The paragraph on page 13, lines 8-21 has been amended as follows:

RNA Isolation and RT-PCR

RNA from frozen excisions was extracted by the guanidinium isothiocyanate, acid phenol method. Samples were immediately dissolved in guanidinium. cDNA was made with random hexamers and BRL Superscript reverse transcriptase. PCR was performed at 57° C. for 40 cycles with the following primers to human Gli1, Gli1-U: CAGAGAATGGAGCATCCTCC (SEQ ID NO:1) and Gli1-D: TTCTGGCTCTTCCTGTAGCC (SEQ ID NO: 2) yielding 412 bp product; to human Gli3, Gli3-U: GCAGCCACAGAATGTCC (SEQ ID NO: 3) and Gli3-D: AGGGATATCCAATCGAGGAATCG (SEQ ID NO: 4) yielding 1 293 bp product; to human Shh, Shh-U2: GAAGATCTCCAGAAACTCC (SEQ ID NO: 5) and Shh-D: TCGTAGTGCAGAGACTCC (SEQ ID NO: 6) yielding a 233 bp product; and to mouse S17 which works well with human cDNA, S17-U: GCTATGTCACGCATCTGATG (SEQ ID NO: 7) and S17-D: CCTCAATGATCTCCTGATC (SEQ ID NO: 8) yielding a 137 bp product. The RT-PCR Shh clone used to make RNA probes derived from a reaction using Shh-U1: AGATGTCTGCTGCTAGTCC (SEQ ID NO: 9) and Shh-D.

IN THE CLAIMS:

Claim 9 has been amended as follows:

9. (Amended) A pharmaceutical composition for the treatment of cellular debilitations, derangements and/or dysfunctions and/or other disease states in mammals caused by the development and presence of sporadic basal cell carcinoma, comprising a therapeutically effective amount of [a material selected from the group consisting of] inhibitors of the expression and activity of Gli1, [their complements or fragments thereof, and mixtures thereof, or a specific binding partner thereto;] and a pharmaceutically acceptable carrier therefor[.], wherein said inhibitors are selected from the group consisting of small molecule

antagonists of Gli1 expression and activity, ligands of Gli1, and agents that exhibit mimicry to Gli1.